REMARKS

This paper is being filed in response to the Office Action mailed on March 21, 2003. A Request for a Three-month Extension of Time is filed concurrently herewith, extending the period of response from June 21, 2003 to September 21, 2003. Claims 77-99 were pending in the application. By this amendment, claims 78, 85, and 87 have been amended, and new claims 100 through 106 added. Claims 77-106 are now pending.

Corrected Inventorship

1. On February 24, 2003, Applicants filed a Request for Deletion of Inventors Under 37 CFR §1.48(b), acknowledgment of that Request and the correct inventorship is respectfully requested.

Election/Restriction

1. Applicants appreciate the Examiner's acknowledgement of the election of Group XVIII (claims 37, 39-40) and the indication that pending claims 77-99 are drawn to the invention of that group.

Specification

2. The Action alleges that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §120. Applicants have amended the first paragraph of the specification to properly include all relevant details of the priority claim. Although the priority claim was made in the declaration filed in the parent case, a copy of which was filed in the present case, some information was unavailable at the time of the original

parent filing. The amended first paragraph sets forth this information and other corrections, such as inclusion of the status of each non-provisional application. Applicants respectfully request recognition of each priority claim.

3. The Action alleges that the title of the invention is not descriptive. Applicants amend the title in accordance with the Examiner's helpful suggestion to read:

NUCLEIC ACID ENCODING HUMAN G PROTEIN-COUPLED RECEPTOR

4. The Action objects to the Abstract of the disclosure because there is no mention therein of polynucleotides encoding G protein-coupled receptors. Applicants hereby amend the Abstract, with a clean copy appearing on a separate sheet. The Abstract now reads:

> The invention disclosed in this patent document relates to transmembrane receptors, more particularly to endogenous, human orphan G protein-coupled receptors. The invention provides, in part, polynucleotides encoding the endogenous, human orphan G protein-coupled receptors.

Claim objections

5. The Action objects to claim 87 as being in improper form because a multiple dependent claim shall not serve as a basis for any other multiple dependent claim. Claim 87 has been amended to remove the multiple dependency. New claims 100 and 101 have been added to represent the subject matter canceled by deletion of the multiple dependency. No new matter has been added.

Claim rejections-35 U.S.C. §101

6. The Action alleges that "the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." On this basis, claims 77-99 were rejected under 35 U.S.C. §101 (lines 5-6 on page 4) and under 35 U.S.C. §112 (line 6 on page 6).

Applicants respectfully assert that an asserted specific and substantial utility as well as a well-established utility for the claimed isolated polynucleotide encoding a GPCR wherein the polynucleotide encodes SEQ ID NO. 20, or the polynucleotide comprises SEQ ID NO 19 is present in this case.

According to MPEP § 2107.02, the Office must presume Applicants' asserted utility is sufficient absent evidence of a reason to suspect otherwise. The Court of Customs and Patent Appeals stated in *In re Langer*:

> As a matter of Patent Office practice, a specification which contains a disclosure of utility which corresponds in scope to the subject matter sought to be patented must be taken as sufficient to satisfy the utility requirement of § 101 for the entire claimed subject matter unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope.

In re Langer, 503 F.2d at 1391, 183 USPQ at 297 (emphasis in original). The MPEP continues, stating:

> Thus, *Langer* and subsequent cases direct the Office to presume that a statement of utility made by an applicant is true. See *In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995).

The burden is upon the Office to provide evidence showing a reason to question Applicants' asserted utility. MPEP § 2107.02 continues to provide guidance in stating:

> in deference to an applicant's understanding of his or her invention, when a statement of utility is evaluated, Office personnel should not begin by questioning the truth of the statement of utility. Instead, any inquiry must start by asking if there is any reason to question the truth of the statement of utility. * * * This means that if the applicant has presented facts that support the reasoning used in

> asserting a utility, Office personnel must present countervailing facts and reasoning sufficient to establish that a person of ordinary skill would not believe the applicant's assertion of utility. *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). The initial evidentiary standard used during evaluation of this question is a preponderance of the evidence (i.e., the totality of facts and reasoning suggest that it is more likely than not that the statement of the applicant is false).

Thus, to establish lack of utility, the Action must provide evidence to contravene Applicants' assertion of utility. Applicants respectfully submit the Action presents no such evidence. Furthermore, even if Applicants' asserted utility were deficient, at the time of filing (and it was not), the hARE-2 GPCR had a well-established utility. MPEP 2107.02(b) indicates that even in the absence of statements asserting a specific and substantial utility, "if an invention has a well-established utility, rejections under 35 USC 101 and 35 USC 112, first paragraph, based on lack of utility should not be imposed. *In re Folkers*, 344 F.2d 970, 145 USPQ 390 (CCPA 1965)."

In support of its utility rejection, the Action relies, in part, on Skolnick et al. [Nature Biotechnology (2000) 18:283-287; "especially page 286, middle of column 1," directed to references #53 and #54] to argue that functional information (*e.g.*, classification of a polypeptide as a G protein-coupled receptor) can be derived from "structural" information only to a limited extent. According to the Action's rationale, "knowledge of the overall structure or domain family is still not enough to confidently assign function to a protein." Importantly however, the Examiner provides helpful hints to meeting the utility requirement. In particular, page 5, lines 17-20 state:

> Therefore, there is little doubt that, after further characterization, the protein encoded by the claimed nucleic acid is found to be member of the GPCR family, the claimed protein would have a specific, substantial and credible utility.

The Action continues, noting that the characterization is part of the invention and that the claimed invention cannot be supported until such a characterization is made.

Applicants respectfully submit that they have made such a characterization. Applicant discloses hARE-2 to be a G protein-coupled receptor (GPCR) selectively expressed in the substantia nigra (see Table C, page 27). As discussed in the entirety of the specification, Applicants maintain that the encoded protein is a GPCR. In fact, each of the pending claims clearly recites that the encoded protein is a G protein-coupled receptor (GPCR). (E.g. claim 1: "An isolated polynucleotide encoding a G protein-coupled receptor . . . .") Thus, it is clear that hARE -2 is a GPCR. Thus, Applicants' respectfully assert that by the Action's own terms, set forth on page 5, lines 17-20, a specific, substantial and credible utility exists.

Applicants respectfully assert that the Action's reliance on the Skolnick et al. reference, as well as references #53 [Kasuya et al., J Mol Biol (1999) 286:1673-91] and #54 [Hegyi et al., J Mol Biol (1999) 288:147-64] cited on "page 286, middle of column 1" to support the utility rejection is misplaced. These references discuss the assignment of protein function from structural information (*i.e.*, "transforming structural information into functional information;" Skolnick et al. page 283/left column/second paragraph), wherein structural information refers specifically to *three-dimensional protein folds*. As explicitly acknowledged by the authors (Skolnick et al., page 284/right column/first paragraph; Kasuya et al., page 1674/left column/second paragraph; and Hegyi et al., page 160/left column/third paragraph), the "results are undoubtedly affected to some degree by the biases inherent in the databases, *e.g.*....toward proteins that readily crystallize (Hegyi et al., page 160/left column/third paragraph). Apparently the biases were such as to have precluded discussion of GPCRs by any of these papers.

More to the point, Applicants respectfully submit that these papers are irrelevant, as hARE-2 is disclosed as a G protein-coupled receptor (GPCR) on the basis of *sequence-based bioinformatic analysis*, not on the basis of three-dimensional protein folds. Sequence-based

bioinformatic analysis had already been used with great success at the time of filing to identify orphan GPCRs [Wilson et al., British Journal of Pharmacology (1998) 125:1387-92; page 125/left column/second and third paragraphs, and page 1388/right column/second paragraph].

As directed by MPEP § 2107.02 and *Langer*, the sufficiency of this utility must be presumed absent evidence showing those skilled in the art would question the truth of the assertion.

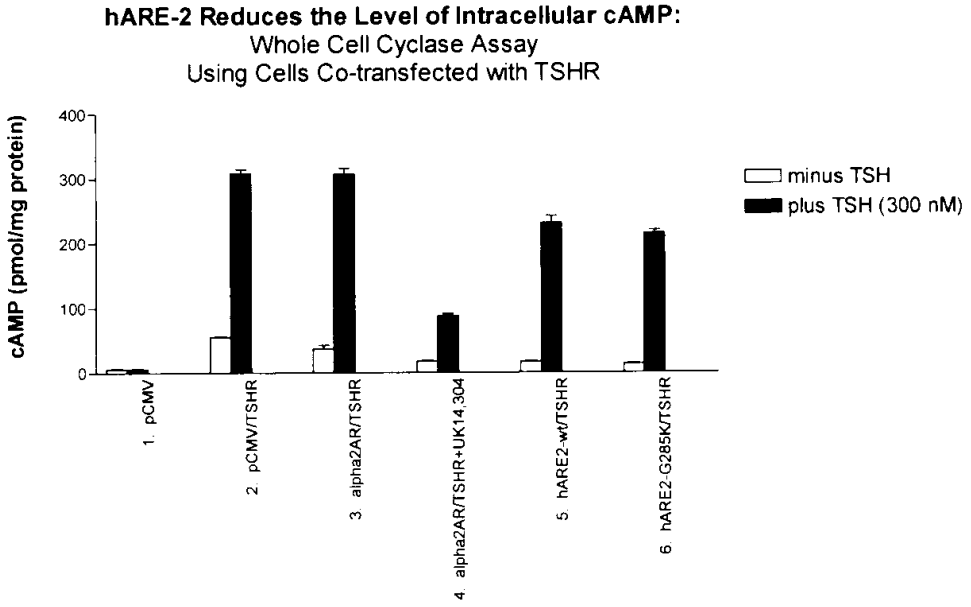
Moreover, even if Applicants' asserted utility is deficient (and, again, it is not), a well-established utility for the hARE-2 GPCR was known at the time of filing. GPCRs are disclosed in the Background section of the specification to modulate the level of intracellular cAMP (see e.g. Applicants' specification, page 12) or the level of intracellular IP3. (see e.g. Applicants' specification, page 13) An elevation of intracellular IP3 was known at the time of filing to lead, in turn, to an elevation of intracellular Ca^{2+} [Berridge, Nature (1993) 361:315-325].

Loss of neurons in the substantia nigra was known at the time of filing to lead to motor impairment, including Parkinson's disease [Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), McGraw-Hill, page 503; filed previously as part of the IDS]. It was further known at the time of filing that the viability of neurons in the substantia nigra is sensitive to the level of intracellular cAMP [Hulley et al., European Journal of Neuroscience (1995) 7:2431-40] and to the level of intracellular $Ca^{2}+$ [Hirsch et al., J Neural Transm Suppl. (1997) 50:79-88].

Thus, at the time of filing, the hARE-2 GPCR, known to be selectively expressed in the substantia nigra, had a well-established utility for the prevention of, and/or for the prevention of exacerbation of, and/or for the treatment of motor impairment, including Parkinson's disease. Applicants respectfully assert that this well-established utility satisfies the utility requirement.

While not required to establish utility for hARE-2 GPCR, but rather to indicate the validity of the asserted and well-established utilities for hARE-2 GPCR, Applicant provides herewith Graph 1 demonstrating a reduction of the level of intracellular cAMP in cells transfected with hARE-2, demonstrating that hARE-2 constitutively couples to Gi.

Graph 1



This graph demonstrates that transient cotransfection of human embryonic kidney (HEK-293) cells with TSHR and a mammalian expression vector pCMV containing endogenous hARE-2 ("hARE2-wt"; experimental group #5) or non-endogenous, constitutively activated hARE-2 ("hARE2-G285K"; group #6) resulted in a respective 25% and 30% reduction of the level of intracellular cAMP proceeding from transfection of Thyroid Stimulating Hormone Receptor alone ("TSHR"; group #2) in the presence of Thyroid Stimulating Hormone (black bars). Gi-coupled alpha2 adrenergic receptor ("alpha2AR") in the presence of alpha2AR agonist UK14,304 was used as a positive control, resulting in a 70% reduction of the level of intracellular cAMP proceeding from TSHR. Empty expression vector ("pCMV") alone was used

as a negative control. Co-transfection of a test construct with the TSHR construct was carried out using equal amounts of DNA.

It necessarily follows that this result also supports the aforementioned well-established utility of hARE-2 relating to motor impairment, particularly Parkinson's disease, conferred in view of the disclosure in the subject application of hARE-2 as a G protein-coupled receptor selectively expressed in the substantia nigra.

Thus, for each of the reasons set forth above, individually and in combination, the utility requirement has been met. Applicants therefore respectfully request withdrawal of the rejection under 35 USC § 101.

Each of the claims was also rejected under 35 USC § 112, first paragraph, for lack of enablement. This rejection was based solely upon the reasoning that where no utility is established, "one skilled in the art clearly would not know how to use the claimed invention." As discussed above, Applicants respectfully assert that a substantial utility has been asserted and that, at the time of filing, there was a well-established utility for the claimed invention.

Accordingly, withdrawal of the 35 USC § 112 rejection is respectfully requested.

Claim rejections-35 U.S.C. §112, first paragraph

7. Claims 78-83 and 85-91 stand rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement in the recitation of the phrase "consisting essentially of." While Applicants assert that those of skill in the art would encounter no difficulty making and using the invention according to the claims as written, claims 78 and 85 nevertheless have been amended to delete the phrase "consisting essentially of" and to assert that the polynucleotide is selected from the group consisting of a) a polynucleotide consisting of a nucleotide encoding the polypeptide of

SEQ ID NO 20, and b) a polynucleotide consisting of the nucleotide sequence of SEQ ID NO 19. Applicants respectfully assert that the amended claims comport with 35 USC § 112, first paragraph, and respectfully request withdrawal of the rejection.

Claim rejections-35 U.S.C. §112, second paragraph

8. The Action also rejects claims 78-83 and 85-91 under 35 U.S.C. §112, second paragraph, for alleged indefiniteness in the recitation of "consisting essentially of." As stated above, Claims 78 and 85 have been amended to overcome these concerns. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 USC § 112, second paragraph.

Conclusion

Early reconsideration and allowance of all pending claims is respectfully requested. If an interview, telephonic or personal, would facilitate allowance of the claims, the examiner is requested to contact Applicants' undersigned attorney.

Respectfully submitted,
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